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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
HANS-ULRICH PETEREIT, ET AL.	: EXAMINER: SASAN, ARADHANA
SERIAL NO: 10/542,283	:
FILED: JULY 15, 2005	: GROUP ART UNIT: 1615
FOR: METHOD FOR PRODUCING AN IMMEDIATELY DECOMPOSING ORAL FORM OF ADMINISTRATION WHICH RELEASES ACTIVE INGREDIENTS	:

DECLARATION UNDER 37 CFR § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

I, Dr. Kathrin Nolkenberger, declare that:

1. I am a graduate of Pharmacy, and received my Pharmacist degree in the year 2004.
2. I have been employed by Evonik Röhm GmbH for 5 years as a pharmacist in the field of Galenic formulation development and melt extrusion
3. That I am familiar with the invention described in the above-identified U.S. Patent Application 10/542,283, filed July 15, 2005.
4. That the following ~~tests were~~ performed ~~by the undersigned, or~~ at my direction, to: (1) Comparative Example 1 was

determine whether a pharmaceutical powder having an average particle size of 200 µm or

less, which immediately disintegrates and releases active ingredient when placed in the mouth, may be produced from a composition comprising (a) an anionic active pharmaceutical ingredient, (b) a copolymer which consists of free-radical polymerized C_1 to C_4 esters of acrylic or methacrylic acid and further (meth)acrylate monomers which have functional tertiary amino groups, (c) 5 to 50% by weight, based on (b), of a C_{12} to C_{22} carboxylic acid; and (d) less than 3% by weight based on the copolymer of an emulsifier having an HLB of at least 14, by spray drying; and (2) compare the disintegration of, the release of active ingredient from, and bitter taste masking characteristics of pharmaceutical powder having an average particle size of 200 μm or less produced from a composition comprising (a) an anionic active pharmaceutical ingredient, (b) a copolymer which consists of free-radical polymerized C_1 to C_4 esters of acrylic or methacrylic acid and further (meth)acrylate monomers which have functional tertiary amino groups, (c) 5 to 50% by weight, based on (b), of a C_{12} to C_{22} carboxylic acid, and (d) less than 3% by weight based on the copolymer of an emulsifier having an HLB of at least 14 which is prepared by melt processing in accordance with the process of Applicant's claims, to the disintegration of, release of active ingredient from, and bitter taste masking characteristics of pharmaceutical powder having an average particle size of 200 μm or less produced from a composition comprising (a) an anionic active pharmaceutical ingredient, (b) a copolymer which consists of free-radical polymerized C_1 to C_4 esters of acrylic or methacrylic acid and further (meth)acrylate monomers which have functional tertiary amino groups, (c) 5 to 50% by weight, based on (b), of a C_{12} to C_{22} carboxylic acid; and (d) less than 3% by weight based on the copolymer of an emulsifier having an HLB of at least 14, which is prepared by spray drying in accordance with the process described by Kajiyama (U.S. Patent 6,656,492, issued December 2, 2003).

5. ~~In~~ As Inventive Example 1, Applicant ~~repeated~~ cites the melt processing procedure of the existing Example 1 of the present Specification (Specification, page 17, lines 18-32) ~~to prepare~~ where a

powder from a composition comprising (a) 16.9 grams of ibuprofen, (b) 1 mol of dimethylaminoethyl methacrylate units contained in the copolymer Eudragit® E PO, 1 mol of stearic acid, and 0.18 mol. of talc, as prepared.

In Comparative Example 1, Applicant attempted to prepare a powder from the same composition comprising (a) 16.9 grams of ibuprofen, (b) 1 mol of dimethylaminoethyl methacrylate units contained in the copolymer Eudragit® E PO, 1 mol of stearic acid, and 0.18 mol. of talc by a spray drying procedure in accordance with the teaching of Kajiyama (U.S. Patent 6,656,492, issued December 2, 2003).

Inventive Example 1 (not newly performed)

39.42 g of Eudragit® E PO (a copolymer powder with an average particle size of 15 μm prepared from methyl methacrylate, butyl methacrylate, and dimethylaminoethyl methacrylate in the ratio 25:25:50), 35.2 g of stearic acid, 16.9 g of ibuprofen, and 8.4 g of talc were put together into an IKA measuring kneader preheated to 100°C. The mixture was kneaded at a product temperature of 100°C for 20 minutes at 60 rpm (2 kneading blades). A powder mixture was removed from the kneader and cooled with dry ice.

Comparative Example 1 (performed)

39.42 g of Eudragit® E PO, 35.2 g of stearic acid, and 16.9 g of ibuprofen were dissolved in 899.28 g of ethanol. 8.4 g of talc was dispersed into the resultant solution. The mixture was processed in a Mini spray dryer (B-290, BUECH) and spray dried under the operational conditions indicated in the following Table 2.

Spray rate	[g/min]	5
Atomizing air vol	[NL/min]	10
Atomizing air press	[bar]	0.8
Inlet air temperature	[°C]	38-56
Outlet air temperature	[°C]	27-34
Air volume (circulation)	[m^3/min]	0.6
Relative humidity at temperature	[%] [°C]	85 5

Table 2: The operational conditions of spray drying process

No powder product could be collected from the spray-dried composition. No spray dried powder could be collected in the collection bin. The inside of the chamber (drying zone) was coated with a very sticky polymer layer.

Different spray drying operational conditions were tested without being able to successfully produce a powder from the mixture. Various attempts to produce a powder by spray drying further diluted mixtures also were not successful. No powder product could be collected by spray drying the mixture of Comparative Example 1 or further dilutions thereof.

6. Results

(a) Inventive Example 1: A powder mixture was produced by melt processing. One gram of the product was placed in the mouth. The product did not taste bitter after two minutes in the mouth, (see example 1 of the present application).

(b) Comparative Example 1: No powder mixture could be collected by the spray drying process. No powder mixture could be collected in the collection chamber of the spray drier even though the operational conditions of the spray drier were varied. No powder mixture could be collected by the spray drying process even though the composition was further diluted. Thus, taste masking could not be tested for any powder produced by the spray drying process of Comparative Example 1. No powder product could be obtained by spray drying.

7. Conclusion

The experimental evidence shows that spray drying and melt processing are not equivalent or alternative processes for producing pharmaceutical powders comprising (a) an anionic active pharmaceutical ingredient, (b) a copolymer which consists of free-radical polymerized C_1 to C_4 esters of acrylic or methacrylic acid and further (meth)acrylate monomers which have functional tertiary amino groups, (c) 5 to 50% by weight, based on (b), of a C_{12} to C_{22} carboxylic acid; and (d) less than 3% by weight based on the copolymer of an emulsifier having an HLB of at least 14. The experimental evidence shows that pharmaceutical powders which immediately disintegrate, release active ingredient, and effectively mask the bitter taste of ibuprofen can be produced from (a) an anionic active pharmaceutical ingredient, (b) a copolymer which consists of free-radical polymerized C_1 to C_4 esters of acrylic or methacrylic acid and further (meth)acrylate monomers which have functional tertiary amino groups, (c) 5 to 50% by weight, based on (b), of a C_{12} to C_{22} carboxylic acid; and (d) less than 3% by weight based on the copolymer of an emulsifier having an HLB of at least 14 by melt processing. The experimental evidence shows that pharmaceutical powders which immediately disintegrate, release active ingredient, and effectively mask bitter taste of ibuprofen could not be produced from (a) an anionic active pharmaceutical ingredient, (b) a copolymer which consists of free-radical polymerized C_1 to C_4 esters of acrylic or methacrylic acid and further (meth)acrylate monomers which have functional tertiary amino groups, (c) 5 to 50% by weight, based on (b), of a C_{12} to C_{22} carboxylic acid; and (d) less than 3% by weight based on the copolymer of an emulsifier having an HLB of at least 14 by spray drying.

8. The undersigned declares further that all statements made herein are known or believed to be true; and further that these statements were made with the knowledge that willful false statements made are punishable by fine or imprisonment, or both, under Section

1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

U. Nolleseph
Signature

25th January 2010
Date

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